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# Pharmacokinetics and safety of tobramycin administered by the PARI eFlow® rapid nebulizer in cystic fibrosis☆

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**Abstract**

*Background:* Nebulization times have been identified as an issue in patient compliance with tobramycin solution for inhalation (TSI) therapy in cystic fibrosis (CF).
*Methods:* In this randomized, open-label, multicentre, two-period, crossover study, patients ($n=25$) with CF and chronic pulmonary pseudomonal infection received TSI for 15 days via eFlow *rapid* or LC PLUS nebulizer. Nebulization times and sputum/serum tobramycin concentrations were determined, and safety evaluated.
*Results:* Nebulization times were significantly shorter for eFlow *rapid* versus LC PLUS on Day 1 (least squares mean estimate of the difference −10.5 min, 95% confidence intervals [CI] −12.6, −8.3, $p<0.0001$) and Day 15 (difference −7.7 min, 95% CI −9.0, −6.5, $p<0.0001$). Broadly comparable sputum/systemic exposure to tobramycin was observed and the incidence of adverse events was similar for both nebulizers.
*Conclusion:* Use of the eFlow *rapid* nebulizer reduced TSI nebulization time. The systemic exposure to tobramycin appeared to be broadly similar in this exploratory study.


*Keywords:* Tobramycin solution for inhalation; Cystic fibrosis; Chronic infection; Nebulization; Pharmacokinetics; *Pseudomonas aeruginosa*

## 1. Introduction

Outcomes in patients with cystic fibrosis and chronic pulmonary pseudomonal infection can be improved by the daily use of nebulized anti-pseudomonal antibiotics, especially tobramycin [1]. The current standard-of-care is nebulized tobramycin solution for inhalation 300 mg in 5 ml (TSI; TOBI®, Novartis Pharma AG) [2]. This solution is specifically formulated for the lung in terms of osmolality and pH to facilitate the delivery of high concentrations of the antibiotic to the site of infection in the endobronchial space, while minimizing the systemic exposure and organ toxicities associated with parenteral aminoglycosides [3]. Intermittent TSI twice daily is effectively administered via a nebulizer, and there is a substantial body of published evidence showing that it is well tolerated, improves pulmonary function, decreases sputum density of *Pseudomonas aeruginosa*, and reduces the incidence of hospitalizations in children and

☆ Previous presentation of data. A summary of the results of this trial have been posted to the Novartis Clinical Trial Results Database. The data have been presented previously as a poster at the 30th European Cystic Fibrosis Conference (ECFC), 13–16 June 2007, Belek, Turkey.

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adults with cystic fibrosis and pulmonary pseudomonal infection [1,4–7].

A long nebulization time may adversely impact on adherence to the regimen [8]. In the case of the PARI LC® PLUS jet nebulizer (PARI GmbH, Starnberg, Germany), powered by the DeVilbiss Pulmo-Aide® compressor (DeVilbiss, Philadelphia, USA), the typical time to deliver the recommended 300 mg dose of tobramycin is 12–15 min [9]. In patients with cystic fibrosis, there is a need for faster [10], more convenient delivery systems, particularly because of the regular use of multiple drugs and inhaled products. One such approach currently in development is tobramycin inhalation powder, a novel dry-powder formulation designed to deliver a high payload of tobramycin topically to the lungs [11]. Alternatively, faster nebulization times may be achieved by more rapid nebulization or the use of more concentrated solutions. PARI GmbH have developed the PARI eFlow® *rapid* nebulizer [12], a highly efficient and fast method to administer inhaled medications [13]. The eFlow *rapid* nebulizer is a soft-mist electronic device designed to deliver liquid solution and suspension products using a vibrating membrane to generate an aerosol with a high percentage of droplets in the respirable size range.

The present study was performed to evaluate the nebulization time, sputum and serum pharmacokinetics and safety of tobramycin delivered as TSI via the eFlow *rapid* nebulizer compared with the LC PLUS nebulizer (the nebulizer currently approved for the delivery of TSI).

## 2. Methods

### 2.1. Study subjects

Eligible patients (≥6 years of age) had confirmed cystic fibrosis (sweat chloride ≥60 mEq/l by the quantitative pilocarpine iontophoresis test and/or genotype with two mutations, plus clinical signs and symptoms) and proven chronic *P. aeruginosa* colonization of the lungs. Other inclusion criteria were: ability to expectorate sputum; forced expiratory volume in 1 s ($FEV_1$) ≥ 25% of calculated value based on age, gender and height [12]; and clinically stable and able to tolerate 1 week without aminoglycoside treatment. The exclusion criteria were: receipt of inhaled or intravenous colistin or other aminoglycosides ≤7 days before TSI administration; receipt of loop diuretics ≤7 days before TSI administration; haemoptysis >60 $cm^3$ ≤30 days before TSI administration; and renal impairment (serum creatinine or blood urea above the upper limit of normal for sex and age or an abnormal urine analysis defined as ≥2+ proteinuria on routine dipstick testing). Written informed consent was required from all patients or legal representatives.

### 2.2. Study design

This exploratory, randomized, open-label, multicentre, two-period, crossover study was performed after a 1-week screening period. In both study periods, patients received tobramycin 300 mg (in the form of TSI 60 mg/ml) twice daily, the approved dose of TSI for patients with cystic fibrosis, for 2 weeks (Days 1–14) plus one TSI dose in the morning of Day 15. Each 15 day treatment was delivered via either the eFlow *rapid* or the LC PLUS nebulizer. After a 1-week TSI-free phase, patients received TSI delivered by the alternative nebulizer for a further 15 days as per the randomized crossover design. Patients were followed for 1 week after the completion of the two TSI administration periods. Compliance was determined by evaluation of the quantity of returned TSI at the end of the study and by diaries completed by the patients. The study, which was approved by the institutional review board of each participating centre, conformed to the ethical principles of the Declaration of Helsinki.

### 2.3. Evaluation of nebulization time and pharmacokinetics

Nebulization times (time from the first tidal breath after the nebulizer was activated until no more TSI could be aerosolized) were recorded on Days 1 and 15 in the clinic and on other days by patients in diaries provided. Nebulization is complete when the nebulizer becomes dry and automatically stops (eFlow *rapid*) or when the nebulizer begins to splutter and nebulization is stopped manually (LC PLUS). Patients attended at clinic on Days 1 and 15, of both study periods, to determine first-dose and steady-state pharmacokinetics of tobramycin in sputum and serum. Sputum samples were expectorated with deep coughing, after gargling with 30 ml of normal saline, twice for 5–10 s, to avoid contamination of the sputum sample with inhaled tobramycin in the buccal cavity. Sputum samples were collected immediately before the start of nebulization (0 h) and 0.5, 1.5, 2 and 8 h after completion of nebulization. Venous blood samples were collected immediately before the start of nebulization (0 h) and 0.5, 1, 1.5, 2, 4 and 8 h after completion of nebulization.

Tobramycin concentration in sputum was determined by reversed-phase high-performance liquid chromatography on a Nova-Pac C18 4 μm (150×3.9 mm) column at room temperature using an isocratic elution (water/acetonitrile [39/61, volume/volume] with 0.2% glacial acetic acid) at a flow rate of 1.5 ml/min, with ultraviolet detection at 360 nm. The lower limit of quantification was 20 μg/g. Tobramycin concentration in serum was determined by fluorescence polarization immunoassay, with a lower quantification limit of 0.05 μg/ml [14]. The area under the tobramycin concentration–time curves (sputum and serum) from 0 to 8 h after the start of nebulization ($AUC_{0-8}$), maximum tobramycin concentrations ($C_{max}$), and time to $C_{max}$ ($T_{max}$) were determined using standard non-compartmental methods. The accumulation ratio was the geometric mean ratio of $AUC_{0-8,Day\ 15}$:$AUC_{0-8,Day\ 1}$.

### 2.4. Safety evaluation

The following three criteria were used to assess safety: (1) potential for systemic toxicity, defined as unusually high concentrations of serum tobramycin (>2 μg/ml in samples collected prior to treatment [trough], >12 μg/ml in samples collected 1 h after completion of nebulization [$C_{max}$], and >4 μg/ml in any other sample); (2) incidence of clinically significant bronchospasm, defined as ≥20% decrease in $FEV_1$ observed from predose to 30 min after completion of nebulization; and (3)